

(ii) a polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV),  
wherein the composition induces antibody that recognizes pre-S1 of HBV.

42. (New) An immunogenic composition according to claim 41 wherein the fusion polypeptide comprises at least 20 contiguous amino acids of the sequence of pre-S1.

43. (New) An immunogenic composition according to claim 41 wherein the fusion polypeptide comprises amino acids 21 to 47 of pre-S1.

*B canceled.*  
44. (New) An immunogenic composition according to claim 41 wherein the polypeptide consisting of at least 6 contiguous amino acids of sequence of tetanus toxin fragment C and the polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of HBV are joined by a hinge linker.

45. (New) An immunogenic composition according to claim 41 wherein the fusion polypeptide comprises at least 100 contiguous amino acids of the sequence of tetanus toxin fragment C. ?

46. (New) An immunogenic composition according to claim 41 wherein the fusion polypeptide comprises full length tetanus toxin fragment C. ?

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REMARKS

Claims 1 to 34 have been canceled without prejudice above and claims 35 to 46 have been added. The claims are supported by, for example, pages 3, 4, and 12 of the specification.

Reconsideration of the application is requested in light of the above amendments and the following remarks.

Election/Restriction

New claims 35 to 46 read on the elected species, a full length of tetanus toxin fragment C fused with 20 amino acids of pre-S1 region of HBV polypeptide. Applicant does not understand the Examiner's requirement to "amend the claims 1-4, 10 and 18 within the full scope of a full length of tetanus toxin fused with peptide encoded by S1 region to reflect the examination on the merits." Page 2, paragraph 6, of October 18, 2001 Office Action. Applicant respectfully requests that the Examiner clarify this requirement if it has not already been complied with by the submission of the new claims.

Claim objections

The Examiner's objection against claim 4 has been rendered moot by the cancellation of the claim.

Rejection under 35 U.S.C. § 112, second paragraph

The rejection relating to the use of the words "region" or "fragment thereof" in the claims has been rendered moot by the fact that these words do not appear in the claims now presented.

The rejection relating to the terms "at least 6 amino acids" and "at least 20 amino acids" of the pre-S region is believed to be unfounded in respect of the claims now presented. The basis of the rejection was that there is no upper limit given in the claims. However, the upper limit is in fact provided by the size of the pre-S1 sequence. The pre-S1 sequence of hepatitis B virus is 119 amino acids in length, so the length of the sequence in question has to be from 6 to 119 amino

acids. This is made clear in the specification. For example, the specification states at page 1, lines 20 to 23, that the fusion protein of the invention may contain “the pre-S1 region” or “a fragment thereof”, and it is clear from this that Applicant envisages that the fusion polypeptide of the invention can contain the whole of the pre-S1 region. Furthermore, the specification states at page 3, lines 27 to 30, that the fusion polypeptide may include a fragment of pre-S1 spanning any section of pre-S1 from amino acids 1-19 to amino acids 100-119, and it is clear from this that the fusion polypeptide may contain any section of pre-S1 from the start of pre-S1 to the end of pre-S1. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

Applicant has now cancelled the claims to a “vaccine” and added claims to “an immunogenic composition” (new claims 41 to 46).

The specification is enabling in respect of the immunogenic compositions now claimed. The Examiner’s attention is drawn in particular to Example 3 on page 17 of the specification and Figures 2 to 5. Example 3 describes experiments in which fusion polypeptides of the invention were administered to mice and the total antibody responses to fragment C or pre-S sequence were determined by ELISA. The results are shown in Figures 2 to 5 and reveal that responses were detected against both the fragment C sequence and the pre-S sequence. Thus, the results show that the fusion polypeptides are immunogenic and can be formulated as immunogenic compositions according to the claims. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103

Applicant believes this rejection to be unfounded in respect of the claims now presented and respectfully requests that the Examiner reconsider it.

The specific selection of elements set forth in claim 1 was not obvious. In particular, it was not obvious to combine both fragment C of tetanus toxin and pre-S1 sequence. It certainly was not obvious that this combination would be effective at inducing an antibody response against the pre-S1 component. The level of antibody response induced by the combination is surprising in view of the prior art.

Applicant asked an expert in immunity against hepatitis B, Dr. Mark Page, to review the rejection and the Examiner's reasoning behind the rejection. Dr. Page's comments are set forth in a Declaration from him provided herewith.

As Dr. Page explains in his Declaration, there were a very large number of carriers known in the art. For example, the following had been used as carriers:

keyhole limpet hemocyanin (KLH),  
gelatin,  
albumin,  
ovalbumin,  
casein,  
bovine gammaglobulin (BGG),  
erythrocytes,  
lipopolysaccharide (LPS),  
carboxymethyl cellulose,  
poly-DL-lysine,  
mycobacterial heat shock proteins,  
micelles,  
liposomes,

virosomes,  
immune stimulating complexes (ISCOMs),  
proteosomes,  
β-galactosidase,  
bacterial outer membrane and periplasmic proteins,  
hepatitis B core antigen,  
hepatitis B surface antigen,  
retroviral Gag proteins,  
phage coat proteins,  
retrotransposon Ty protein p1,  
the B subunit of heat labile toxin of *E.coli*, and  
the B subunit of cholera toxin.

The number of known antigenic sequences that could potentially be linked to each of these carriers was even greater than the number of potential carriers. Khan et al. cited by the Examiner by itself lists a very large number of antigenic sequences in the passage bridging pages 5 and 6. It lists antigenic sequences of:

HIV such as HIV-1 and HIV-2, e.g. the CD4 receptor binding site from HIV;  
hepatitis A virus;  
hepatitis B virus;  
human rhinovirus such as type 2 or type 14 rhinovirus;  
herpes simplex virus;  
poliovirus type 2 and 3;  
foot-and-mouth disease virus (FMDV);  
rabies virus;  
rotavirus;

influenza virus;  
coxsackie virus;  
human papiloma virus (HPV), such as HPV type 16 and the E7 protein thereof and fragments of the E7 protein;  
simian immunodeficiency virus (SIV);  
*Bordetella pertussis* such as the P69 protein and filamentous heamagglutinin (FHA);  
*Vibrio cholerae*;  
*Bacillus anthracis*;  
*E.coli* such as the B subunit of heat labile toxin (LTB), the K88 antigens and enterotoxigenic antigens;  
the cell surface antigen CD4;  
*Schistosoma mansoni* such as p28 glutathione S-transferase antigens (p28 antigens);  
flukes;  
mycoplasma;  
roundworms;  
tapeworms;  
*Chalmydia trachomatis*; and  
malaria parasites.

Thus, there were a vast number of combinations of carrier and antigenic sequence that could in theory have been dreamt up by a person skilled in the art. Out of all these possible combinations, there was no motivation in the art whatsoever to focus on both fragment C and pre-S1 and put the two together. This specific selection was not an obvious selection when viewed in the "real life"

context of all the other combinations that a person skilled in the art might in theory have put together.

Applicant submits that the question that has to be decided is not what a skilled person could in theory have done at the priority date, but what he or she would have done. Whilst in theory a skilled person could have chosen to combine fragment C of tetanus toxin and the pre-S1 hepatitis B virus, we submit that he or she would not obviously have done so.

In assessing the question of obviousness, care has to be taken to avoid the use of hindsight. The Examiner's approach necessarily involves selecting a relatively small number of documents out of a vast state of the art, which documents were identified in a search specifically directed at the claimed invention. A skilled person working before the priority date would not have been able to carry out such a search and would not have put together the combination of documents cited by the Examiner; the combination of documents would not have been obvious before the priority date to a skilled person who had no knowledge of the invention.

As explained by Dr. Page in his Declaration, the art of designing vaccines is an empirical art; it is difficult or impossible to predict in advance whether a particular polypeptide will raise a good immune response such as an antibody response. In order to find out whether a polypeptide might raise a good immune response it is necessary to make the polypeptide and test it in animal models. It is generally not possible to predict in advance with any reasonable degree of certainty whether a given polypeptide will work or not.

The unpredictability of the art had manifested itself in the Shi et al. reference cited by the Examiner. As explained in Dr. Page's Declaration, Shi et al. describes fusion of cholera toxin B subunit (CTB) to pre-S2 epitope. However, the

fusion protein produced an extremely low antibody titre against the pre-S region (see paragraph 9 of Dr. Page's Declaration).

Thus, Shi et al. in fact teaches away from the invention. It would have discouraged a skilled person from attempting to fuse HBV pre-S sequences to carrier proteins in the hope of producing an immunogenic composition.

As Dr. Roberts explains, in contrast to Shi et al., the data in the patent application in question show that a good antibody response can be induced against pre-S by the fusion proteins that are the subject of the application. For example, the results presented in Figure 3B of the application show that, seven days after a booster dose, the fusion proteins induced a good antibody titre against a pre-S1 peptide. The titre is of the same order of magnitude as that against the fragment C component of the proteins (see Figure 2B). These results would not have been expected from a reading of Shi et al. and the other references mentioned by the Examiner. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 103.

In view of the above amendments and remarks, Applicant respectfully requests that the objections to and rejections of the claims be withdrawn. It is respectfully submitted that the application is in condition for allowance, and a notice to that effect is requested.

The October 18, 2001 Office Action did not include an initialed copy of the Form 1449 from the February 8, 2001 Information Disclosure Statement. Applicants respectfully request that the Examiner return an initialed copy of this Form 1449. Please call Applicant's undersigned attorney if the February 8, 2001 Information Disclosure Statement did not reach the file.

If any additional fees are due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 16-2312. If a fee is required for

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Applicant: Steven Neville Chatfield  
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an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

Date: April 17, 2002

By



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